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Original Article

EFFECTIVENESS OF *SCYLLA SERRATA* CHITOSAN FOR INCISION WOUND HEALING IN ORAL MUCOSA OF *RATTUS NORVEGICUS*

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ABSTRACT

Objective: To evaluate the effectiveness of *Scylla serrata*–derived chitosan gel in promoting healing of oral mucosal incision wounds in *Rattus norvegicus*.

Methods: Twenty-five male *Rattus norvegicus* were randomly divided into five groups: a positive control group (Gengigel), a negative control group (CMC-Na gel), and three treatment groups receiving 1%, 3%, or 5% chitosan gel. Chitosan concentrations were selected based on prior evidence of therapeutic potential. Incisions were made on the buccal mucosa, and erythema and wound length were assessed on days 1, 3, and 7 post-incision. Erythema data were analyzed using the Pearson chi-square test, while wound length data were evaluated using the Kruskal–Wallis test.

Results: All chitosan gel groups (1%, 3%, and 5%) demonstrated significantly greater reductions in erythema and wound length compared with the negative control group ($p < 0.05$). Among the treatment concentrations, 3% chitosan gel produced the most effective wound-healing response.

Conclusion: *Scylla serrata* chitosan gel effectively reduces erythema and accelerates wound closure in oral mucosal incision wounds of *Rattus norvegicus*, with 3% identified as the optimal concentration for promoting healing.

Keywords: *Scylla serrata* chitosan gel, Oral mucosa incision wound, Wound healing, Erythema, Wound length

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INTRODUCTION

A wound is a break in tissue continuity that occurs due to the presence of several factors which interfere with the body's protection system. Incision wound is one of the types of wounds which most often occur in oral mucosa due to mechanical trauma or surgical procedures [1]. In the field of prosthodontics, incision wound can occur due to surgical procedures, such as dental implant placement, soft tissue management surgery, or pre-prosthetic surgery [2-4]. Incision wound can heal well, but not infrequently can cause complications, such as infections, prolonged pain, ultimately affecting masticatory function and speech due to the imperfect wound healing process [5]. The process of wound healing occurs in four phases: hemostasis, inflammation, proliferation, and remodeling/maturation phase. Each stage occurs continuously and involves cells in the body facilitating hemostasis, fighting infection, forming new capillaries and granulation tissue, undergoing the epithelialization process until the wound closes [6]. The natural progression of wound healing has the potential to be prevented by various factors, including systemic factors such as age, diabetes mellitus, stress, smoking and alcohol, sex hormones, and nutrition, as well as local factors such as insufficient oxygenation, infection, and foreign material [1, 7].

Currently, wound healing agents made from natural substances have begun to be used to facilitate the healing process due to their few side effects and safe usage [8]. *Scylla serrata* was chosen as the source of chitosan due to its relatively high chitin content compared to other crustaceans, typically around 50-60%, so the amount of chitosan obtained is also quite high. Several studies have proven that crab shell waste contains chitin, which can be processed into chitosan through the chitin deacetylation process. This selection is particularly relevant in Indonesia, where the demand for crabs tends to increase every year, which also has an impact on increasing organic waste in the form of crab shells. The utilization of this waste not only helps decrease organic waste but also offers the potential for developing biocompatible materials for medical applications, especially in wound healing process [9, 10].

Chitosan is a natural biopolymer derived from chitin with the formula *N-acetyl-D-glucosamine*, generally found in crustaceans shells, insect cuticles, and on the cell walls of fungi. Several studies have indicated that chitosan has become a promising biomaterial in therapy in the field of dentistry because it has high biocompatibility, biodegradability, bioadhesion, non-toxic, antibacterial, anti-inflammatory, and wound healing properties. Chitosan biopolymer effectively depolymerizes to *release N-acetyl-D-glucosamine* to stimulate inflammatory cells, fibroblast proliferation, angiogenesis, and provide collagen deposits in the wound healing process [11]. Various types and forms of chitosan biomaterials are used in medical fields, such as powder, hydrogel, paste, sheet, solution, sponge, film, fiber, and nanoparticles [12]. Gel is one of the preparation materials that can be used in administering medicine which has advantages such as being easy to use, having good stability and good dispersion among other topical preparations so that it is easier to apply to wound [13].

Numerous studies were conducted to examine the effects of various chitosan gel concentrations on wound healing. The study of Jesus *et al.* indicated that 3% chitosan gel appeared to enhance the post operative recovery, facilitating accelerated wound healing with minimal complications [14]. Syafruddin *et al.* suggested that 5% chitosan gel was effective in increasing the leukocytes count in the healing process of skin incision wounds in white mice [15]. Another study by Lungu *et al.* found that chitosan gel was proven to have low toxicity against fibroblasts in the skin and had antimicrobial activity against pathogens *S. aureus, C. albicans*, and *E. coli* [16]. These conflicting findings highlight the need for further investigation into the most effective concentrations of chitosan gel, particularly in the context of oral mucosa wound healing.

The intention of this study was to examine the effectiveness of *Scylla serrata* chitosan gel on the healing of incision wound in oral mucosa of *Rattus norvegicus* by observing the application of chitosan gel concentration of 1%, 3%, and 5% in the inflammatory phase and proliferation phase as seen from erythema and wound length.

MATERIALS AND METHODS

The methods and protocols used in this study received approval from the Animal Research Ethics Committee (KEPK) at the Faculty of Mathematics and Natural Sciences, Universitas Sumatera Utara (No. 0612/KEPH-FMIPA/2023).

Sumatera Utara No. 0612/KEPH-FMIPA/2023.

Animals preparation

The 25 male of *Rattus norvegicus* used in this study were 12 to 16 w old with a mean body weight of 150-200 g. The rats must be in healthy conditions characterized by active movement, no abnormalities, and never got any treatment. The rats were acclimatized one week before treatment.

Study design and groups

This study conducted was an *in vivo* experiment with posttest-only control group design. The rats were randomized by simple random sampling and divided into five groups, consisting of 5 wistar rats. Group 1 was given gengigel as the positive control, group 2 was given 1% chitosan gel, group 3 was given 3% chitosan gel, group 4 was given 5% chitosan gel and group 5 was given placebo gel as the negative control.

Chitosan and placebo gel preparation

Chitosan powder used in this study was sourced from Pusat Unggulan Iptek (PUI) Kitosan dan Material Maju. The preparation of 1%, 3% and 5% chitosan gel were prepared by dissolving respectively 1, 3 and 5 g of chitosan powder with 87% degree of deacetylation (DD) into 100 ml of 1% acetic acid. Stirring was conducted with a stirrer until homogeneous, while adding NaOH to get a pH in the neutral range. The pH of the final gel measured using a pH meter paper to ensure neutral range. The chitosan gel was prepared without the addition of any cross-linking agents or external additives in order to evaluate the intrinsic bioactivity and wound healing potential of chitosan itself. The placebo gel *carboxymethyl cellulose* (CMC-Na) concentration used in this study was 2%, 2 g of CMC-Na dissolve into 100 ml of hot distilled water, then stirred until homogeneous and became like a gel.

Incision wound procedure

Wistar rats were anesthetized intraperitoneally using ketamine, with the dosage adjusted to the weight of experimental animals to prevent pain during procedures. After that, an incision was made on the rat's right buccal oral mucosa 1 mm in depth and 10 mm in length and using sterile surgical blade no. 15. The incision depth of 1 mm and the length of 10 mm were standardized using a periodontal probe as a calibrated guide during the procedure, ensuring consistent wound depth and length across all experimental groups. After the incision procedure, the wound was irrigated with normal saline 0.9% to clean the incision wound from debris, then dried with sterile gauze and no suturing was done.

Application of gels

Gel was applied directly to the wound with microbrush until the entire wound surface was covered, ensuring the gel contact with the wound. The application of gel begins immediately after the injury, and applied twice a day.

Clinical evaluation of incision wound healing

The clinical evaluation was carried out by observing the erythema and measuring the length of incision wound on the 1st, 3rd, and 7th d post-incision. Erythema was observed visually with the parameters using the erythema score (Kuncari *et al.*), with no erythema the score is 0, on barely visible erythema the score is 1, on clearly visible erythema the score is 2, on moderate the score is 3, and on severe erythema the score is 4 [17]. The length of incision wound was measured with a periodontal probe (UNC15).

Statistical analysis

Erythema scores were analyzed by the Pearson chi-square test. The data of the incision wound was first analyzed with the Shapiro-Wilk test (<50 samples) to determine the normality of the data. The mean of incision wound length was analyzed using the Kruskal-Wallis test due to the distribution of the data were not normal, then the Mann-Whitney test was used to analyze the multiple comparison tests. A p-value of less than 0.05 ($p<0.05$) indicated that the results were significant. Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS) software version 22.

RESULTS

This study was analyzed the effectiveness of chitosan gel on the healing of incision wound by observing the erythema and measuring the length of incision wound. Erythema scores and wound length were observed visually on the 1st, 3rd, and 7th d post-incision.

Erythema

The difference in erythema scores was determined using the Pearson chi-square test, as the analysis focused on evaluating the frequency distribution of ordinal categories across independent groups rather than comparing medians or ranks. Insignificant difference found in erythema scores on the 1st d (table 1), however on the 3rd and 7th d post incision in gengigel group, 1% chitosan gel group, 3% chitosan gel group, 5% chitosan gel group, and placebo gel group have significant differences in the erythema scores.

Table 1: Result of erythema scores for all groups on the 1st d of observation

Groups	n	Erythema score					P-value
		0	1	2	3	4	
		fx(%)	fx(%)	fx(%)	fx(%)	fx(%)	
Gengigel	5	0 (0%)	3(60%)	2(40%)	0 (0%)	0 (0%)	0.238
1% chitosan gel	5	0 (0%)	2(40%)	3(60%)	0 (0%)	0 (0%)	
3% chitosan gel	5	0 (0%)	3(60%)	2(40%)	0 (0%)	0 (0%)	
5% chitosan gel	5	0 (0%)	3(60%)	2(40%)	0 (0%)	0 (0%)	
Placebo gel	5	0 (0%)	0 (0%)	5(100%)	0 (0%)	0 (0%)	

Notes: f(x) represents the frequency of rats; n represents the total of samples

Table 2: Result of erythema scores for all groups on the 3rdd of observation

Groups	n	Erythema score					P-value
		0	1	2	3	4	
		fx(%)	fx(%)	fx(%)	fx(%)	fx(%)	
Gengigel	5	2(40%)	3(60%)	0 (0%)	0 (0%)	0 (0%)	0,040*
1% chitosan gel	5	1(20%)	2(40%)	2(40%)	0 (0%)	0 (0%)	
3% chitosan gel	5	1(20%)	3(60%)	1(20%)	0 (0%)	0 (0%)	
5% chitosan gel	5	2(40%)	3(60%)	0 (0%)	0 (0%)	0 (0%)	
Placebo gel	5	0 (0%)	0 (0%)	5(100%)	0 (0%)	0 (0%)	

Notes: (x) represents the frequency of rats; f(x) represents the frequency of rats; n represents the total of samples; *Pearson Chi-square test indicated significant

Table 3: Result of erythema scores for all groups on the 7th d of observation

Groups	n	Erythema score					P-value
		0	1	2	3	4	
		fx(%)	fx(%)	fx(%)	fx(%)	fx(%)	
Gengigel	5	5(100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0,000*
1% chitosan gel	5	5(100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
3% chitosan gel	5	5(100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
5% chitosan gel	5	5(100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Placebo gel	5	0(1%)	5 (100%)	0 (0%)	0 (0%)	0 (0%)	

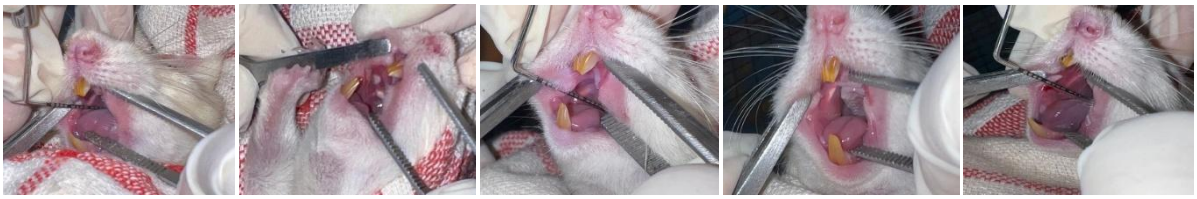
Notes: f(x) represents the frequency of rats; f(x) represents the frequency of rats; n represents the total of samples; *Pearson Chi-square test indicated significant

The results on the 3rd d (table 2), both gengigel and 5% chitosan gel groups showed the greatest decrease in erythema, with only three samples had a score of 1 (barely visible erythema) and two samples had no erythema, with a score of 0 (no erythema). The 3% chitosan gel showed a better reduction in erythema score compared to the 1% chitosan gel group, with only one sample from the 3% chitosan gel group still had a score of 2 (clearly visible erythema), while two samples from the 1% chitosan gel group still had a score of 2 (clearly visible erythema). Meanwhile, all samples from the placebo gel group still showed the same results as on the 1st d observation, with erythema around the wound with a score of 2 (clearly visible erythema).

On the 7th d of observation (table 3), it showed that all samples from the Gengigel group, 1% chitosan gel group, 3% chitosan gel group, 5% chitosan gel group had no erythema, with a score of 0 (no erythema). In contrast, all samples from the placebo gel group still showed slight erythema around the wound, with a score of 1 (barely visible erythema).

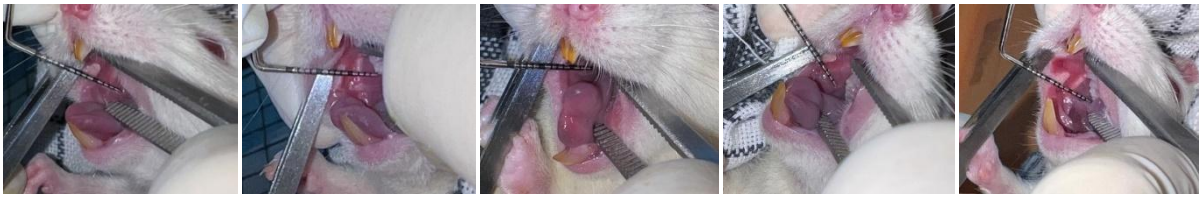
The length of the incision wound

The length of incision wound decreased over time in all groups, especially on the 3rd and 7th d (fig. 2 and 3). Significant differences found on the 3rd and 7th d between Gengigel group, 1% chitosan gel group, 3% chitosan gel group, 5% chitosan gel group, and placebo gel group, but an insignificant difference found on the 1st d of observation (table 4). The condition of incision wound on the 1st, 3rd, and 7th d were represented in fig. 1 to 3.



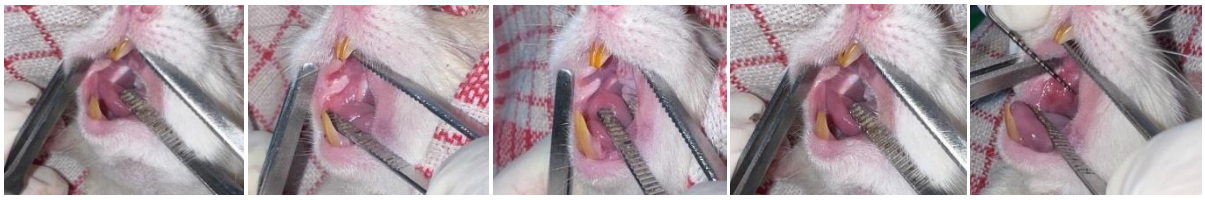
(a) (b) (c) (d) (e)

Fig. 1: Clinical observation of the oral mucosa incision in wistar rats on the 1st d, showing the erythema and wound length conditions in each treatment group (a) Gengigel group; (b) 1% chitosan gel group; (c) 3% chitosan gel group; (d) 5% chitosan gel group; (e) placebo gel group



(a) (b) (c) (d) (e)

Fig. 2: Clinical observation of the oral mucosa incision in Wistar rats on the 3rd d, showing the erythema and wound length conditions in each treatment group (a) Gengigel group; (b) 1% chitosan gel group; (c) 3% chitosan gel group; (d) 5% chitosan gel group; (e) placebo gel group



(a) (b) (c) (d) (e)

Fig. 3: Clinical observation of the oral mucosa incision in wistar rats on the 7th d, showing the erythema and wound length conditions in each treatment group (a) Gengigel group; (b) 1% chitosan gel group; (c) 3% chitosan gel group; (d) 5% chitosan gel group; (e) placebo gel group

Table 4: Result of incision length on the 1st, 3rd, 7th d of observation

Observation	Gengigel (mm)	1% chitosan gel (mm)	3% chitosan gel (mm)	5% chitosan gel (mm)	Placebo gel (mm)	P-Value
Day 1	9,60± 0,55	9,80± 0,48	9,80± 0,48	9,60± 0,55	9,80± 0,48	0.887
Day 3	3,60± 0,89	4,60± 0,55	4,20± 0,84	3,80± 0,45	6,40± 0,55	0,004*
Day 7	0,20± 0,45	0,40± 0,55	0,20± 0,45	0,20± 0,45	1,60± 0,55	0,013*

Notes: *Kruskal-Wallis test indicated significant

Table 5: Multiple comparison of incision length between groups

Groups		Observation		
		Day 1	Day 3	Day 7
Gengigel	1% Chitosan gel	0.513	0.077	0.513
	3% Chitosan gel	0.513	0.268	1
	5% Chitosan gel	1	0.488	1
	Placebo gel	0.513	0,007*	0,011*
1% Chitosan gel	3% Chitosan gel	1	0.419	0.513
	5% Chitosan gel	0.513	0,042*	0.513
	Placebo gel	1	0,007*	0,020*
3% Chitosan gel	5% Chitosan gel	0.513	0.343	1
	Placebo gel	1	0,008*	0,011*
5% Chitosan gel	Placebo gel	0.513	0,006*	0,011*

Notes: *Mann Whitney test indicated significant

The Whitney test (table 5) indicated no significant difference between groups on the 1st d. Meanwhile, on the 3rd d, there were significant differences between the Gengigel with placebo gel group, 1% chitosan gel with 5% chitosan gel group, 1% chitosan gel with placebo gel group, 3% chitosan gel with placebo gel group, and 5% chitosan gel with placebo gel group. On the 7th d, significant differences were found only between the Gengigel with placebo gel group, 1% chitosan gel with placebo gel group, 3% chitosan gel with placebo gel group, and 5% chitosan gel with placebo gel group.

DISCUSSION

Various concentrations of 1%, 3%, and 5% of chitosan gel in this research were selected based on a prior study by de Jesus *et al.*, which indicated that a 3% chitosan gel could reduce redness in patients post tooth extraction [14]. Research by Amer *et al.* also stated that chitosan with concentrations of 1%, 2%, and 3% had the effect of accelerating wound healing, with the most effective concentration of 1% [18]. Another study by Putri *et al.* suggested that 3% and 5% chitosan were effective in fibroblast proliferation and promoting angiogenesis during wound healing but 1% chitosan not able to accelerate fibroblast proliferation [19].

In this study, the erythema scores decreased over time and both the Gengigel group and all chitosan groups showed a greater decrease than the placebo gel group. Pearson Chi-square indicated insignificant differences between groups on the 1st d ($p>0.05$), while significant differences could be seen on the 3rd and 7th d ($p<0.05$). On the 1st d, all samples from the control and treatment groups showed erythema in the incision wound, while on the 3rd and 7th d, only the placebo gel still had erythema in all samples. The insignificant difference on the 1st d could be assumed that during the 1st d of observation, the inflammatory phase began to occur, causing the erythema scores between groups have insignificant differences [20]. However, this study indicated that both the Gengigel and all the chitosan gel groups played a role in reducing signs of inflammation, as evidenced by decreased erythema scores in comparison to the placebo gel group.

The decrease in erythema scores in the treatment groups was related to the ability of chitosan during the inflammatory phase to stimulate inflammatory cells, including macrophages, polymorphonuclear cells (PMN), and fibroblasts [11]. Chitosan works by increasing the infiltration of polymorphonuclear cells which can stimulate the proliferation of macrophages. The *N-acetyl-D-glucosamine* monomer in chitosan binds to the main receptor of macrophages, then be internalized by macrophage cells, thereby triggering migration and proliferation of macrophages [21]. This can enhance the phagocytosis process and the inflammatory phase will soon take place and signs of inflammation will decrease. Chitosan effectively reduces inflammation by decreasing the secretion of key proinflammatory substances, including prostaglandin E2, cyclooxygenase-2 proteins, and cytokines like Tumor necrosis factor alpha (TNF-α) and Interleukin-1 beta (IL-1β). These cytokines play a critical role in promoting vasodilatation and increasing vascular permeability, which are directly responsible for visible signs of inflammation, including redness and swelling. By downregulating these inflammatory signals, chitosan reduces the intensity of erythema observed during the wound healing process. Furthermore, chitosan enhances the expression of Interleukin-10 (IL-10), an anti-inflammatory cytokine that helps regulate the inflammatory response, thereby regulating the inflammatory response and enhancing the healing process. [22]. Jesus *et al.* reported that chitosan gel could reduce redness in patients post tooth extraction, observed on the 2nd and 3rd d. Redness in patients began to decrease progressively, and by the 7th d, all patients who were given chitosan no longer experienced redness [14].

Based on the Kruskal-Wallis test, the length of incision wound on the 1st d showed insignificant differences among the groups, while on the 3rd and 7th d the significant differences began to emerge ($p<0.05$). The insignificant differences on the 1st d were associated with the active inflammation phase, while the significant differences occurred on the 3rd d because the proliferation phase had started, leading to the beginning of wound closure [23].

According to the Mann-Whitney test, the mean of incision wound length between the Gengigel group and the 1%, 3%, 5% chitosan gel group did not show significant difference. However, the significant differences occurred on the 3rd and 7th d of observation between the 1%, 3%, and 5% chitosan group and the placebo gel group. The results of this study indicated that both Gengigel and chitosan gel had the same effect on oral mucosa incision wound healing. This result related that both compounds possess multifunctional bioactive properties that influence key phases of the wound healing process, although their molecular mechanisms differ. It contributes to reducing the inflammatory response, stimulating migration of inflammatory cells and promoting angiogenesis, while the placebo gel group did not contain any compounds that could stimulate the wound healing process [24, 25].

Following the beneficial impact of chitosan during the early stages of wound repair, the reduction of wound length observed in all the chitosan groups may be attributed to chitosan's role in the proliferation phase. During this phase, chitosan release *N-acetyl-β-*

glucosamine, which triggers migration and proliferation of macrophages, causing the stimulation of cytokines and growth factors secretion, such as Platelet-Derived Growth Factor (PDGF), Transforming Growth Factor-β (TGF-β), Fibroblast Growth Factor (FGF), Epidermal Growth Factor (EGF), and Interleukin-1 (IL-1). These factors stimulate collagen secretion and fibroblast proliferation, thereby accelerating re-epithelialization and wound closure [26]. Hartono *et al.* indicated that chitosan gel increased re-epithelialization in rats by enhancing the proliferation and migration of inflammatory cells thereby increasing the secretion of cytokines and growth factors [27].

Chitosan's ability to reduce erythema scores and length of wound closure can also be caused by chitosan's ability as antibacterial. Abedian Z *et al.* showed that both low and high-molecular-weight chitosan has antibacterial properties on oral bacteria [26]. Chitosan's positively charged free amino groups can bind the negative charges from the cell walls of g-negative and g-positive bacteria, which interact on the surface of the bacterial cells and damage the bacterial cell walls [29]. Another theory also explains that chitosan works by entering the nucleus of microorganisms and inhibit the synthesis of proteins and mRNA, which bind to the DNA of microorganisms and prevent the growth of bacteria in the wound [30].

Based on data analysis, the mean length of the incision wound indicated almost no significant difference between 1% chitosan gel, 3% chitosan gel and 5% chitosan gel. The significant difference only occurred between 1% chitosan gel and 5% chitosan gel on the 3rd d of observation the length of the incision wound. However, neither the 3% nor the 5% chitosan showed a significant difference in erythema scores and the length of the incision wound. It could be assumed that the 3% and 5% chitosan gel group had better results compared to the 1% chitosan gel group. This can be caused by the higher the concentration of chitosan, the more hydroxyl groups (-OH) that react, causing cross-linking to be hampered [31]. Bhagawan *et al.* indicated that chitosan concentration that was too high was less able to stimulate various processes in the wound healing pathway [32]. The insignificant differences observed between the 3% and 5% chitosan gel indicated that the 3% chitosan gel is the optimal concentration to use. This is related to the ability of chitosan to form hydrogen bonds with tissue component such as collagen, glycosaminoglycans, and glycoproteins, contributing to its wound healing properties. If the concentration of chitosan is sufficient for these interactions to occur, higher concentrations may not significantly enhance the process, so the concentration of 3% chitosan gel may be sufficient to provide maximum effects on collagen formation, tissue regeneration, and inflammation. Although higher chitosan concentrations generally exhibit increased bioactivity, the 5% gel may have reached a viscosity threshold that hindered effective tissue interaction. This could have limited its ability to penetrate and stimulate cellular processes, making the 3% concentration more optimal for wound healing. The absence of rheological evaluation of the chitosan gels was a limitation of this study, as such data could have clarified the relationship between chitosan concentration and physical properties. This analysis was not included, as the study focused on evaluating the clinical effectiveness of *Scylla serrata* chitosan gel based on erythema and wound length during the inflammatory and proliferative phases. Furthermore, this study did not perform histological analyses, such as the assessment of collagen deposition, fibroblast proliferation and angiogenesis, which could have supported the clinical findings. Future studies are needed to include both rheological and histological evaluations to better clarify the relationship between formulation characteristics and therapeutic effects. Additionally, longer observation periods are needed, as the seven-day observation may not fully reflect the progression of the wound healing process.

CONCLUSION

This study concluded that *Scylla serrata* chitosan gel has proven effective in healing incision wounds on the oral mucosa. The 1%, 3%, and 5% chitosan gel were proven to be effective, which could be shown through reducing erythema and accelerate wound closure in oral mucosa incision wound, but the 3% chitosan gel was the most effective concentration for healing the incision wound indicated by a greater decrease in erythema score and accelerate the wound closure. These findings suggest that *Scylla serrata* chitosan gel, particularly at 3% concentration, has promising potential for clinical application in oral surgery to enhance mucosa wound healing.

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Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally

CONFLICT OF INTERESTS

Declared none

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